**Title: Beyond the controversy on Aβ blood-based biomarkers.**

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## Abstract

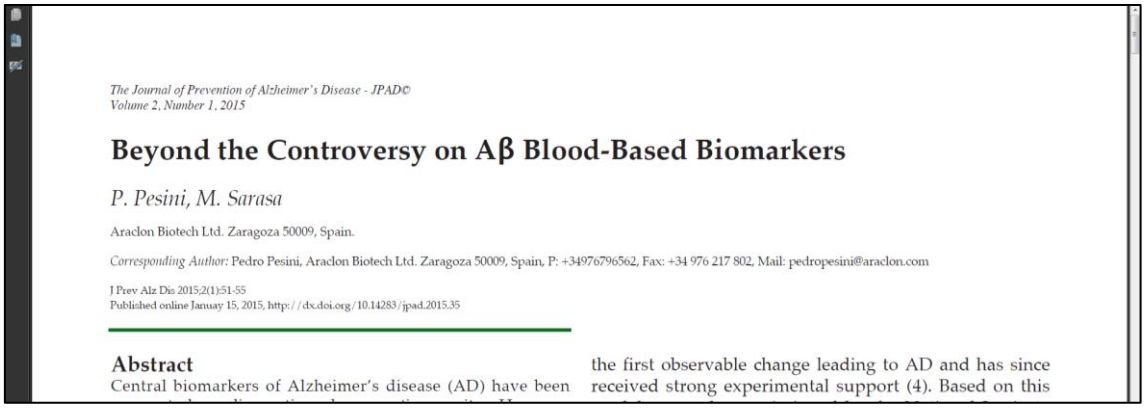
Central biomarkers of Alzheimer's disease (AD) have been proven to have diagnostic and prognostic capacity. However, both amyloid positron emission tomography and cerebrospinal fluid collection studies present problems that limit their widespread acceptability in global clinical trials. Thus, development of other measures as potential surrogates of amyloid positivity should be pursued.

Results from numerous experimental studies strongly suggest that the association between Aβ plasma levels, particularly the Aβ42/Aβ40 ratio, and AD diagnosis goes beyond what could be attributable to pure chance, although this association is still controversial.

The aim of this review is to consider selected works that may help to improve the design of blood based biomarkers studies by controlling a number of confounding sources related to the clinical gold standard, the time-course of central and peripheral biomarkers, and the metabolism of Aβ in blood that may be blurring the presumptive association between Aβ blood levels and AD.

Based on these data and to get pass the controversy, we tentatively postulate that at early stages of preclinical AD, blood Aβ levels and central Aβ biomarkers would follow parallel but temporally displaced trajectories. This association would become eventually lost as the disease progresses and the clearance mechanisms in the blood brain barrier are increasingly impaired.

**Key words:** Alzheimer's disease, plasma, amyloid beta.



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**Beyond the Controversy on Aβ Blood-Based Biomarkers**

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**Abstract**
Central biomarkers of Alzheimer's disease (AD) have been

the first observable change leading to AD and has since received strong experimental support (4). Based on this